

REMARKS

Applicants request entry of the amendments to the specification indicated above pursuant to 37 CFR § 1.71(g)(1), which requires amendment of the specification to disclose the name of each party to the joint research agreement under 35 U.S.C. § 103(c)(2)(C). MPEP § 706.02(I)(2).

Claims 1, 2, 4, 5, and 7-11 are currently pending. Claims 7-11 are withdrawn from consideration. Therefore, claims 1, 2, 4, and 5 are presented for further examination on the merits. Applicants thank the Examiner for reviewing the instant application and respectfully request a further review in light of the comments below.

Rejection under Nonstatutory Double Patenting

The Examiner rejected Claims 1, 2, 4, and 5 on the ground of nonstatutory double patenting over Claims 50-52 of U.S. Patent No. 6,852,742 to Pullela ("Pullela"). According to the Examiner, Claims 1, 2, 4, and 5 would improperly extend the as the right to exclude already granted in Pullela. In particular, the Examiner argues that Claims 1, 2, 4, and 5 essentially teach a species of a disease associated with a cellular calcium channel. *Office Action* at page 4. Furthermore, the Examiner contends that Claim 2 is encompassed by prong b) of Pullela claim 50. Additionally, the Examiner states that there is no apparent reason why applicant was prevented from presenting the instant claims during prosecution of the application which matured into Pullela. *Id.*

The instant application and Pullela were subject to a joint research agreement in effect on or before the date of the present invention under 35 U.S.C. 103(c)(2) and (3). A terminal disclaimer to obviate the nonstatutory double patenting rejection based on activities undertaken within the scope of a joint research agreement in compliance with 37 C.F.R. § 1.321(d) is separately submitted herewith. MPEP § 1490. Applicants therefore respectfully request withdrawal of the rejections.

Rejection under 35 U.S.C. §103(a) based on Pullela

The Examiner rejected Claims 1, 2, 4, and 5 under 35 U.S.C. §103(a) over Pullela. The Examiner argues that Claims 1, 2, 4, and 5 essentially teach a species of a disease associated with a cellular calcium channel. *Office Action* at page 6. Furthermore, the Examiner contends that

Claim 2 is encompassed by prong b) of patented claim 50 in Pullela because of the disclosure drawn to administering an effective calcium-channel antagonizing amount of a compound to the subject. *Id.* The Examiner, however, acknowledged that Pullela does not teach a method for inhibiting calcium T-channel activity. Instead, the Examiner argues that this missing feature is *prima facie* obvious because Pullela discloses a disease associated with a cellular calcium channel, which encompasses the species disclosed in Claim 1 of the instant application. *Id.* According to the Examiner, the motivation to employ Pullela in obviousness over the claimed invention is directed to Pullela teaching the same compound of Formula I for a disease associated with a cellular calcium channel, which reasonably encompasses the instant claim related to selectively inhibiting calcium T-channel activity.

Applicants need not address the Examiner's substantive arguments. Pullela is disqualified as prior art under 35 U.S.C. §103(c) because the subject matter of Pullela and the claimed invention were subject to a joint research agreement at the time the invention was made. MPEP § 706.02(i)(2). Disqualification of a reference under 35 U.S.C. §103(c) as amended by the CREATE Act applies to a reference under 35 U.S.C. §102(e), (f), or (g) and which is being relied upon in a rejection under 35 U.S.C. §103. *Id.* Therefore, Pullela, which was granted on an application filed before the instant claimed invention, is a 102(e) reference that can be disqualified under 35 U.S.C. §103(c).

In order to disqualify a reference under 35 U.S.C. §103(c) as amended by the CREATE Act, an applicant must amend the specification to disclose the names of the parties to the joint research agreement in accordance with 37 C.F.R. § 1.71(g) and a statement complying with 37 C.F.R. § 1.104(c)(4). As noted above, the specification has been amended to state the names of the parties to the joint research agreement in compliance with 37 C.F.R. § 1.71(g). A statement complying with 37 C.F.R. § 1.104(c)(4) is separately submitted herewith. As Applicants have complied with the requirements to disqualify Pullela under 35 U.S.C. §103(c), Applicants request withdrawal of the rejection of Claims 1, 2, 4, and 5 under 35 U.S.C. §103(a) over Pullela.

Rejection under 35 U.S.C. §103(a) based on Kumar, Kobrin, and Li

The Examiner rejected Claims 1, 2, 4, and 5 under 35 U.S.C. § 103(a) as unpatentable over Kumar in view of Kobrin et al. (*Safety of Mibefradil, a New Once-A-Day, Selective T-Type*

Calcium Channel Antagonist, The American Journal of Cardiology, Vol. 80 [48], 1997, printed pages 1-7) (“Kobrin”) and U.S. Patent Publication No. 2001/0049447 to Li et al. (“Li”). Applicants respectfully disagree.

According to the Examiner, Applicants’ previous response to the rejections over Kumar, Kobrin, and Li “is only disagreeable language but no substantial evidence proving nonobviousness over the references cited in the current 103(a) of record. Applicants’ do not clearly address why the references *supra* in the said 103(a) are not obvious.” *Office Action* at page 2 (emphasis added). Applicants respectfully point out that evidence of non-obviousness is already of record in Kumar itself, as Applicants previously explained. Kumar discloses that there are significant differences between L-type (e.g. nifedipine) and T-type (e.g. PPK-5) calcium channel blockers and that the two different types of blockers do not have the same mechanism of action, affinity for the same channel, or activity. Additionally, a person of ordinary skill in the art cannot generalize L-type and T-type blockers with regard to the claimed invention because Kumar (1) discloses that nifedipine and PPK-5 are pharmacologically completely different and (2) does not disclose any *in vivo* treatment, much less a time course. As such, Kumar itself provides evidence of non-obviousness.

Furthermore, the Examiner has not adequately addressed the Applicants’ previous arguments. Characterizing them as “disagreeable language” is not a rebuttal or a substantive consideration of their merit. *Office Action* at page 2. In the absence of a proper rebuttal from the Examiner, the Applicants’ factual and legal arguments stand and have not been shown to be incorrect or insufficient to place the claims in condition for allowance. Applicants respectfully request the Examiner to duly consider the following discussion of the cited references.

To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also* M.P.E.P. § 2143.03. Applicants previously explained and discuss below why combining the disclosures of Kumar, Kobrin, and Li with regard to nifedipine fails to teach or suggest a method for inhibiting calcium T-channel activity comprising the steps of providing a selective T-channel antagonist, as recited in Claim 1.

Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Applicants previously explained and discuss below that the Examiner's articulated reasons why the claimed invention would have been obvious are factually incorrect, thereby providing no reasonable expectation of success.

As explained below in detail, the combination of cited references fail to establish a *prima facie* case of obviousness because they do not teach each and every limitation of the claim and do not provide a reasonable expectation of success for arriving at the claimed invention.

1. The combination of cited references fails to teach each and every limitation of the claims

According to the Examiner, Kumar teaches the claimed elected species by providing the structure represented by PPK 1-16 and PPK-5 in particular. The Examiner also states that Kumar teaches the use of PPK-5 in the blocking of T-Type Calcium Channels. Moreover, the Examiner concludes that Kumar teaches that the elected species and nifedipine have the same mechanism of action, same affinity toward the same receptors, and similar activity. *Office Action* at pages 8-9.

The Examiner notes that Kumar does not teach "prodrug" or "once a day dosing of a T-Type channel antagonist," but asserts Li and Kobrin provide these missing elements, respectively, with regard to nifedipine. The Examiner also characterizes nifedipine as a T-type calcium channel blocker just like the elected species. *Office Action* at page 9. Based on the foregoing premise, i.e., that both the elected species and nifedipine are selective T-type blockers with similar properties, the Examiner concludes that one of ordinary skill would combine the teachings of these references with a reasonable expectation of success. As such, the Examiner concludes that Kumar, Kobrin, and Li establish a *prima facie* case of obviousness. Applicants disagree.

Contrary to the Examiner's contention, the elected species of Claim 1 does not have the same mechanism of action, affinity toward the same receptors, or activity as nifedipine. This is because the elected species is a selective T-type calcium channel blocker and nifedipine is not.

Rather, nifedipine is in fact a selective L-type calcium channel blocker. Although the Examiner in the Office Action characterizes nifedipine as a T-Type blocker, Kumar demonstrates otherwise. Figure 6D of Kumar is a bar graph in log scale comparing the relative selectivities of nifedipine and PPK-5 toward L-type (α_{1L}) and T-type (α_{1D}) Calcium Channels in terms of IC_{50} values. Interpreting the data, Kumar discloses, “Whereas nifedipine blocked L-type channels more effectively than T-type channels by almost 3 orders of magnitude...PPK-5 exhibited a 40-fold selectivity for T-type over L-type channels.” Kumar at page 654, 2nd column (emphasis added). Referring to the side-by-side comparison between nifedipine and PPK-5, Kumar concludes, “Thus, L-type and T-type calcium channels require distinct drug structural requirements for effective DHP block.” *Id.*

Because nifedipine is not a T-type calcium channel blocker, but rather a selective L-type blocker, the data in Kumar are consistent in showing that the elected species and nifedipine actually have a markedly different mechanism of action and activity. The Examiner directed attention to Kumar at page 654, col. 2 to page 655, col. 1, 1st paragraph as teaching similarity of mechanism of action between the claimed compound and nifedipine. The cited passages, however, show the opposite: nifedipine does not block current activity of T-type calcium channels. By contrast, PPK-5 does block T-type calcium channel current activity and is merely antagonized by nifedipine, which increases the PPK-5 time constant approximately twofold.

Far from meaning that the claimed compound and nifedipine have similar mechanism of action or activity, as the Discussion section of Kumar explains, “Thus, we conclude that nifedipine is able to bind to a DHP interaction site on the T-type calcium channel molecule without significantly inhibiting current flux.” Kumar at page 656, 2nd column (emphasis added). Kumar continues to explain, “[W]e favor a model in which the two compounds compete for the same site, but because of its bulkier substituents, PPK-5 is able to effectively block channel activity whereas nifedipine is not.” *Id.* (emphasis added) Although PPK-5 and nifedipine may have an overlapping binding site on T-type calcium channels, Kumar is unambiguous with regard to the fact that PPK-5 has blocking activity whereas nifedipine does not. As such, the claimed compound and nifedipine do not have the same mechanism of action or activity. Notably, the cited passage from the Methods section in Kumar, which the Examiner views as showing that the claimed compound and nifedipine have the same affinity toward the same receptors, does not

even discuss either compound's affinity at all. *See* Kumar, Methods, 2nd col., 1st paragraph (describing synthesis schemes).

In order to establish a *prima facie* case of obviousness, the combination of prior art must teach or suggest all of the elements of a claim. M.P.E.P. § 2142. For the reasons explained above, combining the disclosures of Kumar, Kobrin, and Li with regard to nifedipine fails to teach or suggest a method for inhibiting calcium T-channel activity comprising the steps of providing a selective T-channel antagonist, as recited in Claim 1. The combined cited references with regard to nifedipine do not teach or suggest a selective T-channel antagonist, much less one having an onset of activity in reducing blood pressure in vivo and a duration of activity in vivo, as provided in Claim 1. Indeed, Kumar does not teach any *in vivo* activity of the compounds studied, let alone a time course of *in vivo* activity. Rather, Kumar only discloses *in vitro* data.

Kobrin and Li do not teach or suggest the elements missing from Kumar; including a method for inhibiting calcium T-channel activity comprising the steps of providing a selective T-channel antagonist and administering the selective T-channel antagonist to a mammal in regular doses no more often than once per day. As the combination of Kumar, Kobrin, and Li fail to teach or suggest all elements of Claim 1, Applicants respectfully request the Examiner's rejection of Claim 1 and all claims dependent therefrom be withdrawn.

2. **The cited references provide no reasonable expectation of success because the articulated reasons for why the claimed invention would have been obvious are factually incorrect**

To support a *prima facie* case of obviousness, there must also be a "clear articulation of the reason(s) why the claimed invention would have been obvious." M.P.E.P. § 2142. Here, such requisite articulation is insufficient because the key factual assertion on which the rejection was based is false: nifedipine is not a selective T-type calcium channel blocker. A person of ordinary skill would not have reason to combine the teachings of a selective L-channel antagonist to perform the method of Claim 1, which comprises providing a selective T-channel antagonist having markedly dissimilar mechanism of action and activity according to Kumar.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also* M.P.E.P. § 2143.02.

Here, there is no reasonable expectation of success because the combination of references fails to teach or suggest providing a selective T-channel antagonist, and instead teaches a compound that is selective for a different type of calcium channel and indeed has almost no effect on T-channel current activity. Applicants respectfully request the Examiner's rejection of Claim 1 and all claims dependent therefrom be withdrawn because the combination of references cited in the Office Action fails to establish a *prima facie* case of obviousness.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

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CONCLUSION

Applicant has endeavored to respond to each of the rejections in the outstanding Office Action. In light of the above arguments it is believed that the present application is in condition for allowance. If any questions remain that may be resolved over the telephone the Examiner is hereby invited to telephone the undersigned directly as the number below.

The \$130.00 processing fee set forth in 37 CFR 1.17(i) for the amendment to the specification above is accompanied herewith. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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AMEND

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